Pyruvate Dehydrogenase

Pyruvate to Acetyl-CoA

From cytoplasmic glycolysis, **pyruvate is made** via the **irreversible** enzyme **pyruvate kinase**. "The count" of energy at this point was **+2 ATP** and **+2 NADH**. In the presence of oxygen, pyruvate gets into the mitochondria and becomes acetyl-CoA. It is that step, pyruvate to acetyl-CoA, that we are discussing here.

This reaction has a lot of pieces. The enzyme **pyruvate dehydrogenase** has a lot of parts. The important thing is not the specific enzymatic reactions that happen across the multiple segments involving each cofactor within pyruvate dehydrogenase (the MCAT might test this). That level of detail is atrociously unnecessary. Rather, focus on the importance of the step itself. **Pyruvate dehydrogenase is irreversible**. But more than that, **there is no reaction that can make pyruvate from acetyl-CoA**. The system is locked forward. Acetyl-CoA can do a lot, to be sure. But if we want to go "back up glycolysis" (aka gluconeogenesis), there is going to have to be some pretty elaborate trickery to get back to pyruvate in the cytoplasm.

That is because of just how complex pyruvate dehydrogenase is. At its most fundamental, pyruvate dehydrogenase takes a pyruvate ("pyruvate") and makes NADH ("dehydrogenase"). But unlike most dehydrogenase steps where that is all that happens . . . a lot more is involved than the simple ones in glycolysis that were reversible and glossed-over.

Ins and Outs

The inputs to the system are pyruvate, CoA, and NAD. **Pyruvate** comes from glycolysis. **CoA** comes from the vitamin pantothenate. **NAD** comes from the vitamin **niacin**.

The outputs of the system are acetyl-CoA, NADH, and CO_2.

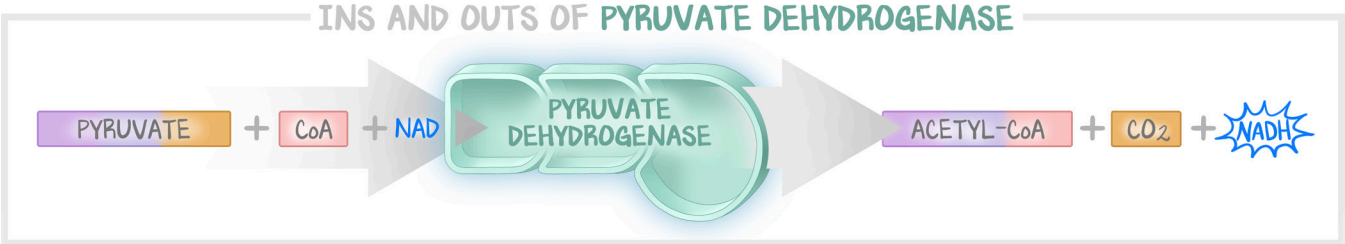

Figure 4.1: Pyruvate Dehydrogenase Ins and Outs
The net input and output of pyruvate dehydrogenase. Most of the substrates in pyruvate dehydrogenase's reaction are recycled, so they are left out of this equation.

That sounds pretty easy, right? Well, why did we mention pantothenate and niacin? Because of the in-betweens.

In-Betweens

Pyruvate dehydrogenase requires five cofactors to work. We already met **CoA** and **NAD**. In addition to these two, we have in this process **thiamine** (vitamin $\mathbf{B_1}$), **lipoic acid** (that we make, so don't have to eat) and **FAD-FADH$_2$** that we get from **riboflavin**. These are cofactors, involved in reactions within pyruvate dehydrogenase that are not worth the time to learn. Thiamine, lipoic acid, and riboflavin are necessary for this system to proceed, but are not consumed in the process.

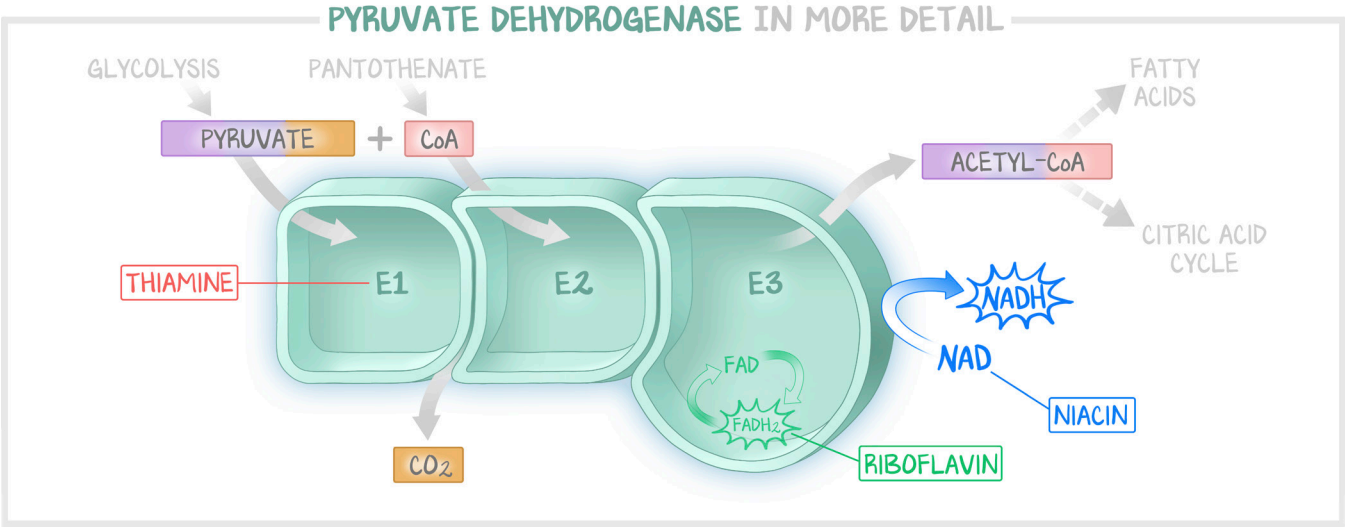

Figure 4.2: Pyruvate Dehydrogenase in More Detail
PDH requires multiple cofactors and multiple steps, despite the inputs and outputs being so "simple."

Thiamine Deficiency

The most clinically relevant of the five cofactors is thiamine. Thiamine deficiency is common in long-term chronic alcoholics who get most of their calories from alcohol. **Alcohol prevents thiamine absorption in the gut**. The vitamin deficiency weakens the ability to utilize pyruvate dehydrogenase. Without thiamine, the rate-limiting step of the Krebs cycle, isocitrate dehydrogenase, fails to go. And lastly, a protein that is involved with metabolism of branched-chain amino acids is compromised by low thiamine. So . . . with no thiamine, pyruvate dehydrogenase can't be used (which makes ATP), the Krebs cycle can't happen (which makes ATP), and energy from amino catabolism is limited (makes ATP). This puts **metabolically active tissue at the highest risk**, especially that tissue which does not store glycogen for use when glucose is depleted. The **heart** and the **brain** meet the requirements of "no glycogen and metabolically active." In a starvation state (when no glucose can be used), fatty acids are broken down by the liver, and they become the primary fuel for the heart and brain. These ketones are acidotic, which also makes encephalopathy and cardiovascular function worse.

The brain. Severe thiamine deficiency can lead to **encephalopathy or coma**. This happens often enough in emergency care to have been propagated into an automatic treatment for being found down, the "coma cocktail." This medley includes naloxone (to reverse opiates) and the combination of **thiamine** and **D50** even in the presence of normal blood sugar. All three have low enough risk to be freely given without a clear diagnosis, and these medications can prove to be both diagnostic and therapeutic. Naloxone does its thing—it works without glucose or thiamine. But to get the D50 to work (if that is the problem) **thiamine must be given first**. If the patient is truly thiamine deficient, addition of glucose (as D50, which is 50% glucose in water) would serve only to add substrate for cytoplasmic glycolysis. Without thiamine, pyruvate dehydrogenase couldn't work, and the patient, despite having ample blood glucose, would not have the ability to use that glucose the way they need to.

Beyond coma, the neurological presentation of thiamine deficiency is described as **Wernicke-Korsakoff Syndrome**. While it's presented as a spectrum of disease, it's easier to see Wernicke's (reversible confusion and ataxia) and Korsakoff's (permanent brain lesions), resulting in Wernicke's + confabulation.

Wernicke's peripheral neuropathy (ataxia, nystagmus, and memory loss) presents like someone who is drunk. They are not drunk, and their blood alcohol content will be normal. At this point, the damage

is reversible with high doses of intravenous thiamine. If allowed to persist, the damage becomes permanent, resulting in **Korsakoff syndrome**. Korsakoff's is characterized by permanent memory loss with confabulation in addition to the ataxia, nystagmus, and cerebellar dysfunction.

The **heart**. "Wet beri-beri" is the term given to **systolic heart failure** as a product of **keto acid accumulation** in cardiac muscle. The heart needs a constant supply of oxygen (since it's always beating). Without thiamine, the only energy the heart can use is keto acids, which keep things going, but poorly. A poorly working heart is a heart in failure. Heart failure symptoms are peripheral edema, crackles, JVD, exertional dyspnea, and orthopnea—processes that arise from being overloaded, also called "wet."

Destiny of Acetyl-CoA

There are many bridges in metabolism, and acetyl-CoA is one of them. Acetyl-CoA plays a pivotal role in gluconeogenesis regulation (Metabolism #8: *Gluconeogenesis*) as well as the formation and catabolism of fatty acids (Metabolism #13: *Lipid Synthesis* and Metabolism #15: *Lipid Catabolism*). But we are going to focus on carbohydrate metabolism and continuation of that metabolism onto the electron transport chain, and so in the next lesson we will talk about how acetyl-CoA enters the Krebs cycle, the citric acid cycle. Acetyl-CoA **can never** be converted into pyruvate. Acetyl-CoA **can never** be turned into glucose. Acetyl-CoA is a molecule that allows for the generation of a lot of energy. Just memorize this fact now; it will make more sense after reviewing gluconeogenesis and lipid metabolism.

Regulation of Pyruvate Dehydrogenase

Pyruvate dehydrogenase is the key step that locks the pyruvate forward towards TCA-ETC. This process generates energy. **Insulin dephosphorylates PDH, activating it**. Insulin does the same thing in the cytoplasm to PFK-2—activation through a dephosphorylation. This happens **only in hepatocytes**—other tissues are regulated by substrate-level regulation only.

For all other cells than the hepatocytes, it's all **substrate-level control**, local to the enzyme. Hepatocytes also have this local substrate-level control in addition to insulin. Pyruvate dehydrogenase is in the mitochondria, so we need to think about what is physically located in the mitochondria that might influence it.

Teleologically, pyruvate dehydrogenase is designed to make energy; to take that pyruvate, turn it into acetyl-CoA; and then generate ATP through the Krebs cycle and the electron transport chain. The end goal is to **make ATP**. ATP is made in the mitochondria. So, then, it makes sense that **lots of ATP** in the mitochondria will **inhibit** pyruvate dehydrogenase.

In the same sense, the **product of the enzyme inhibits the enzyme**. That is, **acetyl-CoA** and **NADH** are directly inhibitory in addition to ATP. Acetyl-CoA, NADH (and $FADH_2$) , and ATP are all considered "high-energy markers," and tend to occur together.

Calcium is **stimulatory**. Calcium? We haven't once mentioned calcium in all of metabolism. What's up with calcium? One, it's the only substrate that **stimulates pyruvate dehydrogenase**, which makes it an exception, and a board favorite. But it also makes sense. If there is much calcium in a muscle cell, it's probably contracting, and, if it's contracting, it's going to need ATP.

In hepatocytes, insulin stimulates PDH through dephosphorylation. In skeletal muscle, calcium stimulates pyruvate dehydrogenase. Everywhere there is pyruvate dehydrogenase, it's inhibited by ATP, acetyl-CoA, and NADH.

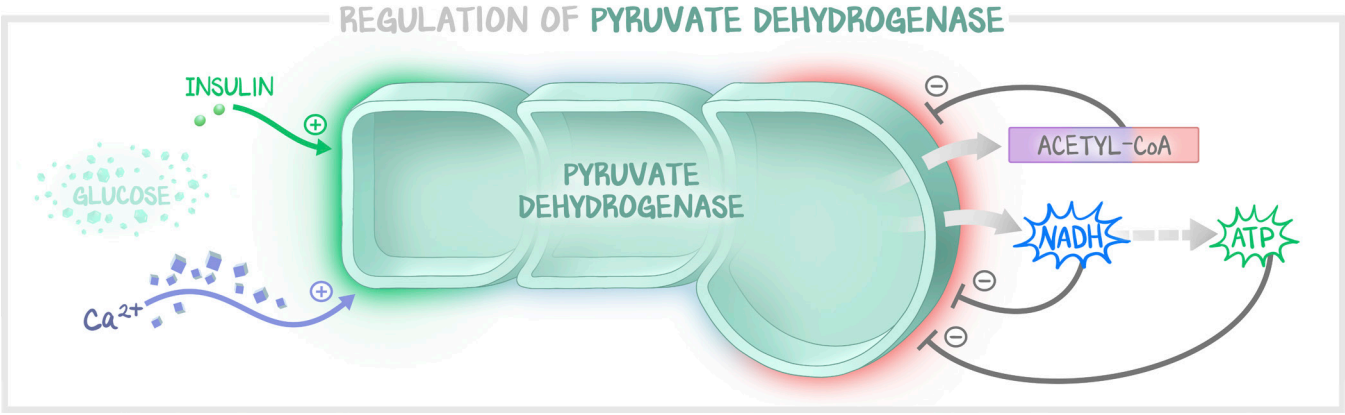

Figure 4.3: Regulation of Pyruvate Dehydrogenase
The regulation is substrate-level (acetyl-CoA, NADH, and ATP) in all cells. Certain tissues have other ways of regulating PDH. For example, the liver uses insulin, and in smooth muscle cells, calcium stimulates PDH.

The Energy Count

For each pyruvate molecule that gets turned to acetyl-CoA, **1 NADH** is made. NADH is high-energy, and that will be sent to the electron transport chain. Since there are **2 pyruvates** for every **1 glucose**, we add **2 NADHs** to the list. The count thus far was +2 ATP and +2 NADHs. The count is now **+2 ATPs** and **+4 NADHs**.